2. RESPONSE/REMARKS

2.1 STATUS OF THE CLAIMS:

Claims 1-36 were pending at the time of the Action.

Claims 22 and 34 have been canceled herein without prejudice or disclaimer.

Claims 1, 2, 5, 9-11, 13-18, 20, 21, 23, 24, 26, 27, 29, 31 and 33 have been amended herein.

Claims 44-51 have been added herein.

Claims 1-21, 23-33, 35, 36, and 44-51 are now pending in the application.

2.2 SUPPORT FOR THE CLAIMS:

Support for the pending claims can be found throughout the original claims, specification and figures as filed. It is Applicants' belief that no new matter is included as a result of the accompanying amendment.

2.3 AMENDMENT OF THE SPECIFICATION OVERCOMES THE DISCLOSURE OBJECTIONS.

The Action at page 2 objected to the disclosure because of informalities over the reference to the drawings throughout the text. Specifically the figure identifiers were corrected throughout the text to conform to the several views of the drawings.

Applicants have overcome the objection by the amendment submitted herewith, and respectfully request that it now be withdrawn.

2.4 A SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT IS PROVIDED.

Applicants enclose herewith a Supplemental Information Disclosure Statement, along with the authorization to charge the Deposit Account for the required fee, making an additional

reference of record in the pending Application. Applicants respectfully request that the SIDS be considered by the Office and so indicated by the Examiner in the next subsequent Action on the merits.

2.5 THE REJECTIONS UNDER 35 U. S. C. § 112, 1ST PARAGRAPH, ARE OVERCOME.

Claims 1-4, 6-19, and 21-32 were rejected under 35 U.S.C. § 112, first paragraph, allegedly as failing to provide an adequate written description of the invention, and allegedly failing to adequately teach how to make and use the invention commensurate in scope with the pending claims.

The Action at page 3 notes that the specification, "while describing and being enabling for determination of skeletal development in pre-adults, and in those suspected of having a skeletal disease or disorder, with determinations of the N-terminal fragment of pro-C-type natriuretic peptide (NT-proCNP) in plasma, does not reasonably provide description or enablement for determinations indicative of skeletal disease or disorders in subjects with biological samples generally."

Applicants respectfully traverse; however, but appreciate the Office's admission that the instant application is fully enabling and contains sufficient written description for many important aspects of the inventors' overall work. To that end, and solely in an effort to advance claims of particular commercial relevance to early allowance, Applicants have provided the accompanying amendment to address the Office's general concern regarding the specificity of the claim language.

Independent claim 1 has been amended to recite:

"(a) method for assessing skeletal growth of a subject other than an adult in congestive heart failure, comprising measuring NT-CNP in a biological fluid from the subject, and comparing this measured level of NT-CNP against a mean NT-CNP level from a control population for which at least a first skeletal growth information is known, wherein a significant deviation in the measured level of NT-CNP in the subject from the mean level of NT-CNP in the control population is indicative of abnormal skeletal growth."

Independent claim 14 has been amended to recite:

"(a) method for predicting skeletal growth potential of a subject other than an adult in congestive heart failure, comprising measuring NT-CNP in a biological fluid from said subject, and comparing this measured level of NT-CNP against a mean NT-CNP level from a control population that has attained maximum skeletal growth and predicting from the NT-CNP level in the subject, skeletal growth potential of the subject."

Independent claim 15 has been amended to recite:

"(a) method for predicting skeletal age of a subject other than an adult in congestive heart failure, comprising measuring NT-CNP in a biological fluid from said subject and comparing this measured level of NT-CNP against a mean NT-CNP level from a control population of known skeletal ages, and predicting from the NT-CNP level in the subject, the skeletal age of the subject.

Independent claim 16 has been amended to recite:

"(a) method for diagnosing a skeletal disease or disorder in a subject other than an adult in congestive heart failure, comprising measuring NT-CNP in a biological fluid from said subject, and comparing this measured level of NT-CNP against a mean NT-CNP level from a control population, wherein a significant deviation in the measured level from the mean control level is indicative of a skeletal disease or disorder."

Applicants believe that these claims, and those that depend therefrom, now recite aspects of the invention that are free from any rejection under the Statutes and are in condition for allowance. Applicants respectfully request, therefore, that the enablement and written description rejections be withdrawn.

In further response to the Office's concern over the clarity of the particular claim language, and mindful of the Office's indication of allowable subject matter on page 3 of the Action, Applicants have also added new independent claims 44 and 48 that respectively recite:

"(a) method for assessing skeletal growth of a pre-adult subject, comprising measuring NT-CNP in a biological fluid from the subject, and comparing this measured level of NT-CNP against a mean NT-CNP level from a control population for which at least a first skeletal growth information is known, wherein a significant deviation in the measured level of NT-CNP in the subject from the mean level of NT-CNP in the control population is indicative of abnormal skeletal growth," and

"(a) method for assessing skeletal growth of a subject suspected of having a skeletal disease or disorder, comprising measuring NT-CNP in a biological fluid from the subject, and comparing this measured level of NT-CNP against a mean NT-CNP level from a control population for which at least a first skeletal growth information is known, wherein a significant deviation in the measured level of NT-CNP in the subject from the mean level of NT-CNP in the control population is indicative of abnormal skeletal growth in said subject."

The former claim encompasses the assessment method in *pre-adult* subjects, while the latter encompasses the assessment method in subjects (either adult or pre-adult) *suspected of having* a skeletal disease or disorder. Dependent claims 45-47 and 49-51 further characterize the step of measuring, by reciting binding between NT-CNP, and an antibody or antibody binding fragment that selectively binds to an NT-CNP peptide, and particularly those antibodies or antibody binding fragments that selectively bind to NT-proCNP peptides such as proCNP(1-103), proCNP(1-50), proCNP(1-81), and proCNP(51-81).

Applicants believe that these new claims, and the respective dependencies, are fully in compliance with all sections of the Statutes, and are therefore now in condition for allowance.

Claims 1-8, 11, 12, 14-21, 24, 25, 28-34 and 36 were rejected under 35 U.S.C. § 112, first paragraph, allegedly because the specification, "while being enabling for anti-NT-proCNP antibodies for use in immunoassays," does not reasonably provide description or enablement for a method or binding means generally, and in particular, for a receptor specific for NT-proCNP.

Applicants respectfully traverse; however, but appreciate the Office's admission that the instant application is fully enabling and contains sufficient written description for the use of antibodies that are specific for NT-CNP peptides in immunoassays to detect the level of NT-CNP protein in a biological fluid. To that end, and solely in an effort to advance claims of particular commercial relevance to early allowance, Applicants have provided the accompanying amendment to address the Office's general concern regarding the specificity of the claim language. The language of claims 21, 23, 24, and 26 has been amended to particularly claim and distinctly point out detection methods for NT-CNP protein that employ antibodies or antibody binding fragments that selectively bind to particular peptides comprising NT-proCNP antigens, including, for example, proCNP(1-50), proCNP(1-103), proCNP(1-50), proCNP(1-81), and proCNP(51-81) peptides.

It is Applicants' belief that the present claim scope is fully supported by the specification as originally filed. One of ordinary skill in the art would be able to follow the teachings set forth in the specification to correlate the levels of NT-CNP, and to make and use the invention commensurate in scope with such claims. In particular, one can measure NT-CNP in a biological fluid, and secondly link such NT-CNP in plasma and other bodily fluids to skeletal status in both adults and pre-adults, without undue experimentation.

In light of the accompanying amendment, Applicants now respectfully request the withdrawal of the rejection.

2.6 THE REJECTION OF CLAIMS UNDER 35 U.S.C. § 112, 2ND PARAGRAPH, IS OVERCOME.

Claims 1-36 were rejected under 35 U.S.C. § 112, 2nd paragraph, allegedly as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as their invention.

Applicants respectfully traverse. However, in an attempt to address each of the Office's concerns, and to further improve the clarity of the pending claims, have incorporated the helpful suggestions of the Examiner to provide better antecedent basis for the rejected claims.

With respect to claims 22 and 34 the rejection is moot, as these claims have been canceled without prejudice or disclaimer in the accompanying amendment.

With respect to the pending claims, the remaining rejections are hereby overcome:

Claim 1 has been amended to provide better antecedent basis.

In claims 13, 26 and 27 "using" has been replaced by "with" per the Examiner's suggestion.

Claims 14-16 have been rewritten to provide clear antecedent basis.

In claim 18, "pro-adult" was replaced by "pre-adult."

Claims 29, 31, 33, and 36 have been amended to clarify antecedent basis, and to overcome a typographical error.

Applicants believe that each of the rejections set forth in pages 4 and 5 of the Action have been addressed in the foregoing amendment, and as such now respectfully request that these rejections be withdrawn.

2.7 THE REJECTION OF CLAIMS UNDER 35 U.S.C. § 102(b) IS OVERCOME.

Claims 1, 2, 6-9, 11-17, 21, 22, 24-28, 33, 34 and 36 were rejected under 35 U.S.C. § 102(b), allegedly as being anticipated by Prickett* et al., (Biochem. Biophys. Res. Comm., *286:513, 2001; hereinafter, "Prickett").

The Action at page 6 considers that the reference teaches "the detection and measurement of the N-terminal fragment of pro-C-type natriuretic peptide (NP-proCNP) in human plasma." The Office contends that the mere recitation of a desired result (in this case, assessing skeletal growth) does not impart novelty to the claims over the scientific paper by Prickett.

Applicants traverse, and respectfully assert that for a reference to legally anticipate a claim, each and every element of the claim must be taught by the cited reference. The reference by Prickett, however, fails in this regard.

Prickett is concerned with the detection and measurement of NT-CNP in plasma of sheep and human patients with congestive heart failure and in healthy controls. While the reference provides an assay for *quantitating* NT-CNP levels in a biological fluid sample, and suggests that high levels of the protein can be indicative of congestive heart failure, Prickett does not teach or suggest any method for *correlating* a given level of NT-CNP from a biological fluid taken from a test subject and comparing it to the NT-CTP levels in a control population for which one has skeletal growth information, to assess, or predict, skeletal growth in the test subject. Moreover, Prickett does not teach or suggest a method for assessing skeletal growth of a subject, comprising measuring NT-CNP in a biological fluid from the subject, and comparing this measured level of NT-CNP against a mean NT-CNP level from a control population for which at least a first skeletal growth information is known, wherein a significant deviation in the measured level of

NT-CNP in the subject from the mean level of NT-CNP in the control population is indicative of abnormal skeletal growth.

There is also *no teaching or suggestion* in Prickett that provides any method for assessing skeletal growth of a subject other than an adult in congestive heart failure, comprising measuring NT-CNP in a biological fluid from the subject, and comparing this measured level of NT-CNP against a mean NT-CNP level from a control population for which at least a first skeletal growth information is known, wherein a significant deviation in the measured level of NT-CNP in the subject from the mean level of NT-CNP in the control population is indicative of abnormal skeletal growth. The Action at page 8 confirms Applicants' position: The teachings of Prickett "differ from the invention as instantly claimed in not teaching monoclonal antibodies specific for proCNP and in not specifically exemplifying determinations in patients with suspected skeletal diseases."

Only the methods set forth in the present application compare the relevant amounts of NT-CNP in test subjects to those in control subjects for the purpose of assessing skeletal growth.

With respect to claims 22 and 34 the rejection is moot, as these claims have been canceled without prejudice or disclaimer in the accompanying amendment.

With respect to the pending claims, the rejection is overcome because Prickett fails to teach each and every element of the claimed invention, and as such, cannot legally anticipate the invention.

As such, Applicants respectfully request that the rejection now be withdrawn.

2.8 THE REJECTION OF CLAIMS UNDER 35 U. S. C. 103(a) IS OVERCOME.

Claims 1-36 were rejected under 35 U.S.C. § 103(a), allegedly as being legally obvious over Prickett in view of Buechler* et al. (U.S. Pat. Appl. Publ. 2003/0219734, *hereinafter, "Buechler"), and Yasoda* et al. (J. Bone Min. Res., *15[Suppl. 1]:S243, 2000; hereinafter "Yasoda"), further in view of Chusho* et al. (Proc. Natl. Acad. Sci. USA, *98:4016, 2001; hereinafter, "Chusho").

Applicants respectfully traverse.

The Supreme Court has repeatedly concluded that a finding of obviousness is a question of law based on "underlying factual inquiries." The relevant factors to be considered were set forth over forty years ago in *Graham* v. *John Deere Co.* (383 U.S. 1, 148 USPQ 459, 1966) as follows: (a) determining the scope and content of the prior art; (b) ascertaining the differences between the claimed invention and the prior art; and (c) resolving the level of ordinary skill in the pertinent art.

These same *Graham* factors have also been applied in *each* of the Supreme Court's subsequent decisions regarding obviousness, including the widely-publicized *KSR International Co.* v. *Teleflex Inc.* [See *e.g., United States* v. *Adams, 383 U.S. 39, 51–52, 148 USPQ 479, 483 (1966); Sakraida* v. *Ag Pro, Inc.*, 425 U.S. 273, 189 USPQ 449, reh'g denied, 426 U.S. 955 (1976); *Dann* v. *Johnston*, 425 U.S. 219, 189 USPQ 257 (1976); *Anderson's-Black Rock, Inc.* v. *Pavement Salvage Co.*, 396 U.S. 57, 163 USPQ 673 (1969) and *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. _, 82 USPQ2d 1385 (2007)][1].

[1]""In *United States* v. *Adams*, [t]he Court recognized that when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result. In *Anderson's-Black Rock, Inc.* v. *Pavement Salvage Co.*, [t]he two [pre-existing elements] in combination did no more than they would in separate, sequential operation. [I]n *Sakraida* v. *AG Pro, Inc.*, the Court derived the conclusion that when a patent simply arranges old elements

In *KSR*, the Supreme Court concluded that the district court had correctly determined that the patent-in-suit was invalid as obvious, and that the Federal Circuit had erred in its decision (*Teleflex Inc.* v. *KSR Int'l Co.*, 119 Fed. Appx. 282, 288 [Fed. Cir. 2005]) overturning the lower court's finding by applying its longstanding "teaching-suggestion-motivation ("TSM") test" in an "overly rigid and formalistic way."

In *KSR*, the Supreme Court reaffirmed the familiar framework for determining obviousness as set forth in *Graham* based on its precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." The Supreme Court further stated that:

> "[w]hen a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, 35 U. S. C. § 103 bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill."

When considering obviousness of a combination of known elements, the operative question is thus ''whether the improvement is more than the predictable use of prior art elements according to their established functions."

Following the decision in *KSR,* the Office published revised examination guidelines on October 10, 2007 [Fed. Reg. **72(195)**:57526-57535] to assist Examiners in determining obviousness under 35 U.S.C. § 103 in view of the Supreme Court's latest decision. The revised guidelines note that when resolving the *Graham* inquiries,

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with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious."" (*Id.* p. 57527; internal quotations omitted).

> *"[i]t must be remembered that while the ultimate determination of obviousness is a legal conclusion, the underlying Graham inquiries are factual. When making an obviousness rejection, Office personnel must therefore ensure that the written record includes findings of fact concerning the state of the art and the teachings of the references applied. In certain circumstances, it may also be important to include explicit findings as to how a person of ordinary skill would have understood prior art teachings, or what a person of ordinary skill would have known or could have done. Factual findings made by Office personnel are the necessary underpinnings to establish obviousness."*
>
> *"In short, the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge. This is so regardless of whether the source of that knowledge and ability was documentary prior art, general knowledge in the art, or common sense."*

In *KSR Int'l. Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007), the Court stated that "a patent composed of several elements *is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.* Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important ***to identify a reason*** *that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.* This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.* at 1741 (emphasis added).

As the PTO recognizes in M.P.E.P. § 2142:

> "... [T]he examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of non-obviousness..."

If, however, the Examiner does produce a *prima facie* case, the burden of coming forward with evidence or arguments shifts to the applicant who may submit additional evidence of non-obviousness, showing that the claimed invention possesses improved properties not expected by the prior art. The initial evaluation of *prima facie* obviousness thus relieves both the Examiner and applicant from evaluating evidence beyond the prior art and the evidence in the specification as filed until the art has been shown to suggest the claimed invention:

> *"To reach a proper determination under 35 U.S.C. § 103, the Examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the Examiner must then make a determination whether the claimed invention as a whole would have been obvious at that time to that person. Knowledge of Applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention. The tendency to resort to hindsight based upon Applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art"* (emphasis added). M.P.E.P. § 2142.

Similarly, as the Federal Circuit observed in its decision of *In re Oetiker*:

> *"The ultimate determination of patentability is based on the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence. The legal standard of "a preponderance of evidence" requires the evidence to be more convincing than the evidence which is offered in opposition to it. With regard to rejections under 35 U. S. C. § 103, the Examiner must provide evidence which as a whole shows that the legal determination sought to be proved (i.e., the reference teachings establish a prima facie case of obviousness) is more probable than not"* (emphasis added). In re Oetiker, *977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992).*

In the present application, Applicants respectfully assert that the legal standard required

for sustaining a rejection of the pending claims for obviousness as a matter of law has not been met. Moreover, Applicants believe that the cited references also fail to obviate the claimed invention based upon matters of fact.

M.P.E.P. § 2143.01(III) states that "the mere fact that references *can be combined* does not render the resultant combination obvious *unless the results would have been predictable* to one of ordinary skill in the art." In the present case, the Office has not provided any evidence or clear reasoning why combining the teachings of Prickett with those of Buechler, Yasoda or Chusho in *any* way would present a predictable result, or render the claimed invention legally obvious.

The Office has not shown how it would have been obvious to one of ordinary skill in the art that the combination of the four cited references would have provided a *predictable* result in a method for assessing skeletal diseases or disorders. The Office considers only that the references *could* be combined in some fashion so as to make the invention obvious to one of ordinary skill in the art; not how combining these teachings *would* have caused one of ordinary skill in the art to achieve the claimed methods *predictably*, and without any further improvement, assessment, development or experimentation. For this reason alone, the Examiner's burden of factually supporting a *prima facie* case of obviousness has not been met, and as such the rejection under 35 U.S.C. § 103(a) should be withdrawn.

Buechler is said on page 7 of the Action to teach "elicitation of antibodies, polyclonal, monoclonal, recombinant, or antigen-binding fragments thereof, to peptide fragments of C-type natriuretic peptide comprising at least 6 contiguous amino acids for assays, such as sandwich immunoassays in which a first antibody is bound to a solid surface, for determination of the peptide fragments in a sample, such as blood, serum, or plasma."

Yasoda is said on page 7 of the Action to "teach skeletal overgrowth in transgenic mice that overexpress C-type natriuretic peptide and Chusho *et al.*, teach dwarfism in knockout mice lacking C-type natriuretic peptide expression."

The Action contends that "it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have substituted monoclonal antibodies and alternative assay formats such as sandwich immunoassays, as taught in Buechler, for the polyclonal antibodies and competitive assay in Prickett *et al.* because to do so is notoriously old and well known in the art."

Applicants respectfully disagree, and further assert that Buechler discloses antibodies that detect degradation products of natriuretic peptides (such as BNP, ANP, CNP, etc.) in describes their use in ***more accurately diagnosing cardiovascular disease***. Buechler neither teaches nor discloses any use of such antibodies to *assess skeletal growth, skeletal status, or skeletal disorder*. Applicants further note that although the Prickett reference was cited in the application by Buechler (see, *e.g.*, Col 2, line 3), no mention was made in Buechler of NT-CNP, NT-BNP, or NT-ANP, and no mention was made of their use in any assay described by Buechler. Moreover, there is no mention in Buechler to make or use *any* antibodies that selectively bind to NT-CNP, NT-BNP, or NT-ANP, much less any of the antibodies described in Prickett, in *any* method for assessing skeletal growth, skeletal status, or skeletal disorder. The combination of references is completely silent as to the presently claimed methods.

Moreover, *no* mention is made in Buechler of the specific peptide fragments disclosed in Prickett --namely, proCNP(51-103), proCNP(82-103) and proCNP)1-15)-- making it clear to the Applicants that even though Buechler *et al.* were aware of (and cited) the earlier work by Prickett in their Application, Buechler clearly was not motivated by, and did not contemplate

making or using, any antibodies to the peptide fragments disclosed in Prickett. Had Buechler and co-workers been motivated in some fashion to include aspects of the Prickett reference, it certainly would have been made apparent in Buechler's application for patent. That it did not convinces Applicants that not even Buechler *et al.* themselves were motivated to combine the disparate teachings of the two separate lines of research, much less a random ordinarily-skilled artisan that *read* the Prickett and Buechler references.

More importantly, however, even if, *in arguendo*, the teachings *were* somehow combined, the result would still not achieve the claimed subject matter. Even if one of ordinary skill in the art *were* to have combined the teachings of Buechler and Prickett, and or even if they were viewed with the additional disclosures set forth in Yasoda and/or Chusho, one would still only have been motivated to use anti-CNP antibodies *to more accurately diagnose congestive heart failure*, and not to assess or predict skeletal growth, skeletal status, and/or any skeletal disorders. As such, Applicants believe that the present obviousness rejection clearly fails the standard set forth in both *Graham* and in *KSR*, and as such, should now be withdrawn.

2.8.1 A DECLARATION UNDER 37 C.F.R. § 1.132 IS PROVIDED.

The Office has concluded that one of ordinary skill would not only have been motivated to combine the teachings of the four disparate references to produce the claimed invention, ***but also to do so with the expectation of success, and with an ability to predict the outcome of the invention***. The Office concludes that the claimed methods for assessing skeletal growth as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made in view of the disclosure of Prickett when considered in view of the references by Buechler, Yasoda, and Chusho.

Again, Applicants respectfully traverse.

In further response to these rejections, Applicants believe that the Office is using the impermissible benefit of hindsight reconstruction, selectively choosing excerpts from the cited references to advance rejection of various pending claims based upon legal obviousness using the cited references.

Applicants enclose herewith (as **Exhibit A** and containing an Appendix A therein) a Declaration under 37 C.F.R. § 1.132 from inventor Timothy Charles Ramsey Prickett that provides additional scientific evidence to address the assertions set forth in the present Action.

In particular, panels A and B of FIG. 1 of Dr. Prickett's Declaration address the concern that the only biological fluids in which the present methods had been employed were plasma or whole blood. These data demonstrate that (a) NT-CNP is also detectable in urine, and (b) the levels of NT-CNP in biological fluids (including urine and serum) correlates with the skeletal status of an individual. As one example, the Declarant notes that higher levels of NT-CNP were observed in biological fluids taken from children, than from biological fluids taken from adults.

FIG. 2 of the accompanying Inventor Declaration also provides further scientific data illustrating that an increase in plasma NT-CNP levels and bone alkaline phosphatase in adult sheep follows the administration of the hormone estrogen, which has been shown to stimulate new bone formation in the adult skeleton. Together, these findings provide demonstrable evidence that the level of NT-CNP, when compared to an appropriate control, can be used to measure the impact of agents capable of affecting the skeletal status of adults.

An additional example demonstrating the use of the claimed methods for assaying NT-CNP and correlating its level in a test subject as compared to control subjects (in which at least a

first skeletal growth information is known), to diagnose one or more skeletal disorders in a subject, including adults, is shown in FIG. 3 of the attached Inventor Declaration.

Using a well-established animal model of mild osteoarthritis, a significant increase in plasma NT-CNP occurs three months after induction of focal articular cartilage trauma. This increase in NT-CNP, reflecting chondrocyte proliferation in response to injury, coincides with other biochemical changes in collagen products, as measured in synovial fluid collected from the affected arthritic joint.

It was not known until the present invention that circulating NT-CNP levels could be correlated with skeletal growth. The inventors surprisingly discovered that this correlation holds true throughout all distinct phases of human growth (neonatal, childhood, and pubertal). Moreover, surprisingly the level of NT-CNP was predictive not only of skeletal growth potential of a subject, but also the attainment of final adult height in an individual subject (see, *e.g.,* the ROC curve in FIG. 4 of the accompanying Inventor Declaration).

Further, the inventors have discovered **high** levels of NT-CNP in blood samples collected from a subgroup of children with extreme short stature, yet **low** skeletal growth rates. This subgroup of children has a block to the action of CNP within the bone growth plate, and can now be effectively diagnosed using the methods of the present invention by the high level of NT-CNP (see, *e.g.,* FIG. 5 of the accompanying Inventor Declaration).

Another surprising discovery of the inventors was the finding of **high** levels of NT-CNP in subjects with distorted bone overgrowth associated with chromosomal abnormalities. This is also demonstrated in FIG. 5 of the accompanying Inventor Declaration. Now, and for the first time, diagnosis of these disorders is possible by the finding of a high NT-CNP level in subjects that demonstrate suspicious patterns of bone overgrowth as observed, *e.g.,* on X-ray.

There was no teaching or suggestion in any of the cited prior art documents that the level of circulating NT-CNP corresponded to skeletal growth rate; all that had been previously reported was that CNP acted *in vivo* locally (*i.e.,* at the site of bone growth) to stimulate bone growth. There was no motivation or expectation of success for a person of ordinary skill in the art, prior to the present invention, to combine the cited references in any combination to produce the claimed invention. As such, the obviousness rejection over these references is improper, and Applicants respectfully request that it be withdrawn.

2.8.2 ADDITIONAL SCIENTIFIC EVIDENCE BY THE INVENTORS AND CO-WORKERS IS PROVIDED.

Applicants also note the Action's contention that there has not been evidence presented that correlates NT-CNP levels in adults with skeletal status. Applicants respectfully disagree, and note that not only did the original specification teach the use of its methods in assessing adults' (as well as pre-adults') skeletal status (Specification at FIG. 11A and FIG. 11B), but additional scientific evidence was collected by the inventors and their co-workers that demonstrated NT-CNP levels in adults reflected change in skeletal status.

To supplement the data presented in the original specification and the accompanying Inventor Declaration, Applicants also further attach hereto (as **Exhibit B,** containing FIG. 6A and FIG. 6B) a summary of *additional* scientific data obtained by Inventor Prickett and his co-workers that further indicate that NT-CNP and alkaline phosphatase (a marker of new bone formation), respectively, were reduced in adult sheep by the steroid dexamethasone, which was well-known to those of ordinary skill in the art to inhibit bone formation in the adult skeleton.

These data were subsequently published (as FIG. 4) in a manuscript accepted for publication by the scientific journal, *Pediatric Research*[2].

These data, combined with the original teachings set forth in the specification and those presented in the accompanying Inventor Declaration, provide further scientific evidence that the combination of references relied upon by the Office to support a rejection of obviousness is insufficient to either anticipate, or render obvious, the claimed methods. Likewise, these data evidence Applicants' belief that the skilled artisan would have lacked a reasonable expectation of success in achieving the claimed methods for assessing skeletal function simply by combining the disparate disclosures of Prickett, Buechler, Yasoda, and Chusho.

To that end, Applicants again respectfully request that the pending rejections be withdrawn.

2.9 CONCLUSION

It is respectfully submitted that all claims are fully-enabled by the Specification, that all pending claims are definite, and that the inventions embodied in those claims are useful, novel, and non-obvious. Applicants believe that the claims are acceptable under all sections of the Statutes and are now in condition for ready allowance. Applicants earnestly solicit concurrence by the Examiner and the issuance of a Notice of Allowance in the case with all due speed. Applicants note for the record their explicit right to re-file claims to one or more aspects of the invention as originally claimed in one or more continuing application(s) retaining the priority claim from the present and parent cases.

[2]A copy of the report as published (*Pediat. Res.*, 58(2):334-340, 2005) is attached hereto as **Exhibit C**.

Should the Examiner have any questions, a telephone call to the undersigned Applicants' representative would be appreciated.

Respectfully submitted,

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Facsimile: 214-200-0853

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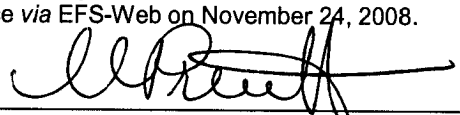

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